At page 121, line 12, please delete "C (asp)" all three occurrences and substitute therefor --C (ala)--.

At page 122, line 11, please delete "C (asp)" all three occurrences and substitute therefor --C (ala)--.

IN THE CLAIMS:

Please cancel claims 1-62 without prejudice.

Please add new claims 63-163 as follows consistent with the restriction requirement mailed on December 10, 1997 in the above identified parent application.

Sub B1

--63. An isolated infectious recombinant respiratory syncytial virus (RSV) comprising a RSV genome or antigenome, a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase protein (L), and a RNA polymerase elongation factor, wherein a modification is introduced within the genome or antigenome comprising a partial or complete gene deletion, a change in gene position, or one or more nucleotide change(s) that modulate expression of a selected gene.

64. The recombinant RSV of claim 63, wherein said gene is selected from an attachment (G) protein, fusion (F) protein, small hydrophobic (SH) protein, RNA binding protein (N), phosphoprotein (P), large polymerase protein (L), M2(ORF1) or M2(ORF2) product, matrix (M) protein, or a nonstructural protein NS1 or NS2.

A2

65. The recombinant RSV of claim 63, wherein a RSV gene is deleted in whole or in part.

66. The recombinant RSV of claim 65, wherein a SH, NS1, NS2, or G gene is deleted in whole or in part.

67. The recombinant RSV of claim 66, wherein the SH gene is deleted.

68. The recombinant RSV of claim 66, wherein the NS1 gene is deleted.

69. The recombinant RSV of claim 66, wherein the NS2 gene is deleted.

70. The recombinant RSV of claim 63, wherein expression of a selected RSV gene is reduced or ablated by introduction of one or more translation termination codons.

71. The recombinant RSV of claim 70, wherein expression of a selected RSV gene is reduced or ablated by introduction of multiple translation termination codons.

72. The recombinant RSV of claim 71, wherein expression the RSV NS2 gene is reduced or ablated by introduction of multiple translation termination codons

73. The recombinant RSV of claim 63, wherein expression of a selected RSV gene is reduced or ablated by introduction of a frame shift mutation in the gene.

74. The recombinant RSV of claim 63, wherein expression of a selected RSV gene is modulated by introduction, modification or ablation of a translational start site within the gene.

75. The recombinant RSV of claim 74, wherein a translational start site of the selected gene is modified or ablated to prevent efficient translation initiation at said start site.

76. The recombinant RSV of claim 74, wherein an internal translational start site of the selected gene is modified or ablated to prevent efficient translation initiation at said start site.

77. The recombinant RSV of claim 74, wherein an internal translational start site of the RSV G gene is ablated to prevent efficient translation initiation at said start site specifying expression of a secreted form of the G protein.

78. The recombinant RSV of claim 74, wherein a translational start site is introduced upstream of the selected gene or internally to enhance expression of the gene.

79. The recombinant RSV of claim 63, wherein a position of one or more gene(s) in the genome or antigenome is altered relative to a RSV promoter.

80. The recombinant RSV of claim 79, wherein a position of said one or more gene(s) is changed to a more promoter-proximal location specifying enhanced expression of the gene(s).

81. The recombinant RSV of claim 80, wherein said position of said one or more gene(s) is changed to a more promoter-proximal location by deletion of coding or non-coding sequences within the genome or antigenome upstream of said one or more gene(s).

82. The recombinant RSV of claim 81, wherein positions of multiple RSV gene(s) are changed to a more promoter-proximal location by deletion of a SH or NS2 gene or genome segment.

83. The recombinant RSV of claim 79, wherein a position of said one or more gene(s) is changed to a more promoter-distal location specifying reduced expression of the gene(s).

84. The recombinant RSV of claim 81, wherein a coding or non-coding polynucleotide sequence selected from an autologous or heterologous RSV or non-RSV gene or gene segment is inserted in the genome or antigenome upstream of said one or more gene(s).

85. The recombinant RSV of claim 79, wherein positions of multiple genes in the genome or antigenome are altered by changing their relative gene order.

86. The recombinant RSV of claim 85, wherein the positions of multiple genes are altered by reciprocal positional substitution of said genes in the genome or antigenome.

87. The RSV of claim 86, wherein the NS2 gene is reciprocally substituted in position for the SH gene.

88. The recombinant RSV of claim 63, wherein said modification within the genome or antigenome comprising a partial or complete gene deletion, a change in gene position, or one or more nucleotide change(s) that modulate expression of a selected gene specifies a change in phenotype for the resultant recombinant virus selected from a change in growth characteristics in culture, small plaque size, attenuation in vivo, temperature-sensitivity, cold-adaptation, host range restriction, change in antigen expression, or a change in immunogenicity.

89. The recombinant RSV of claim 63, wherein the genome or antigenome is further modified to incorporate one or more attenuating mutation(s) present in one or more biologically derived mutant human RSV strain(s).

90. The recombinant RSV of claim 89, wherein the genome or antigenome is further modified to incorporate at least one and up to a full complement of attenuating mutations present within a panel of biologically derived mutant human RSV strains, said panel comprising cpts RSV 248 (ATCC VR 2450), cpts RSV 248/404 (ATCC VR 2454), cpts RSV 248/955 (ATCC VR 2453), cpts RSV 530 (ATCC VR 2452), cpts RSV 530/1009 (ATCC VR 2451), cpts RSV 530/1030 (ATCC VR 2455), RSV B-1 cp52/2B5 (ATCC VR 2542), and RSV B-1 cp-23 (ATCC VR 2579).

91. The recombinant RSV of claim 89, wherein the genome or antigenome is further modified to incorporate at least one and up to a full complement of attenuating mutations specifying an amino acid substitution at Val267 in the RSV N gene, Glu218 and/or Thr523 in the RSV F gene, Cys319, Phe 521, Gln831, Met1169, Tyr1321 and/or His 1690 in the RSV polymerase gene L, and a nucleotide substitution in the gene-start sequence of gene M2.

92. The recombinant RSV of claim 89, wherein the genome or antigenome is further modified to incorporate at least one mutation specifying a temperature-sensitive substitution at amino acid Phe521, Gln831, Met1169, or Tyr1321 in the RSV polymerase gene or a temperature- sensitive nucleotide substitution in the gene-start sequence of gene M2.

93. The recombinant RSV of claim 89, wherein the genome or antigenome incorporates at least two attenuating mutations.

94. The RSV of claim 1, having at least three attenuating mutations.

95. The recombinant RSV of claim 89, wherein the genome or antigenome includes at least one attenuating mutation stabilized by multiple nucleotide changes in a codon specifying the mutation.

96. The recombinant RSV of claim 63, wherein the genome or antigenome comprises a partial or complete human RSV genome or antigenome of one RSV subgroup or strain combined with a heterologous gene or gene segment from a different, human or non-human RSV subgroup or strain to form a chimeric genome or antigenome.

97. The recombinant RSV of claim 96, wherein the heterologous gene or gene segment is from a human RSV subgroup A, human RSV subgroup B, bovine RSV, or murine RSV.

98. The recombinant RSV of claim 96, wherein the heterologous gene or gene segment is selected from a RSV NS1, NS2, N, P, M, SH, M2(ORF1), M2(ORF2), L, F or G gene or gene segment.

99. The recombinant RSV of claim 96, wherein the chimeric genome or antigenome comprises a partial or complete human RSV A subgroup genome or antigenome combined with a heterologous gene or gene segment from a human RSV B subgroup virus.

100. The recombinant RSV of claim 99, wherein the heterologous gene or gene segment from human RSV B encodes a RSV F, G or SH glycoprotein or a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof.

101. The recombinant RSV of claim 100, wherein one or more human RSV B subgroup glycoprotein genes F, G and SH or a cytoplasmic domain, transmembrane domain, ectodomain or immunogenic epitope thereof is substituted within a partial RSV A genome or antigenome.

102. The recombinant RSV of claim 101, wherein both human RSV B subgroup glycoprotein genes F and G are substituted to replace counterpart F and G glycoprotein genes in the RSV A genome or antigenome.

103. The recombinant RSV of claim 96, wherein the chimeric genome or antigenome comprises a partial or complete human RSV B subgroup genome or antigenome combined with a heterologous gene or gene segment from a human RSV A subgroup virus.

104. The recombinant RSV of claim 63, wherein the chimeric genome or antigenome comprises a partial or complete RSV background genome or antigenome of a human or bovine RSV combined with a heterologous gene or genome segment of a different RSV to form a human-bovine chimeric RSV genome or antigenome.

105. The recombinant RSV of claim 104, wherein the heterologous gene or genome segment is substituted for a counterpart gene or genome segment in a partial RSV background genome or antigenome.

106. The recombinant RSV of claim 104, wherein the heterologous gene or genome segment is added adjacent to or within a noncoding region of the partial or complete RSV background genome or antigenome.

107. The recombinant RSV of claim 104, wherein the chimeric genome or antigenome comprises a partial or complete human RSV background genome or antigenome combined with a heterologous gene or genome segment from a bovine RSV.

108. The recombinant RSV of claim 63, wherein the genome or antigenome is further modified to incorporate a nucleotide deletion, insertion, substitution, rearrangement, or modification of a cis-acting regulatory sequence within the recombinant RSV genome or antigenome.

109. The recombinant RSV of claim 108, wherein the cis-acting regulatory sequence occurs within a 3' leader, 5' trailer or intergenic region of the RSV genome or antigenome.

110. The recombinant RSV of claim 108, wherein the cis-acting regulatory sequence is a gene-start (GS) signal, a (GE) signal, or a RSV promoter element.

111. The recombinant RSV of claim 108, wherein the cis-acting regulatory sequence is a gene-start (GS) or gene-end (GE) signal which is modified, deleted, inserted or is replaced by a heterologous GS or GE signal in the genome or antigenome.

112. The recombinant RSV of claim 111, wherein a GE signal of the RSV NS1 or NS2 gene is replaced by a corresponding GE signal of the RSV N gene.

113. The recombinant RSV of claim 108, wherein the cis-acting regulatory sequence is replaced by a heterologous regulatory sequence.

114. The recombinant RSV of claim 113, wherein the heterologous regulatory sequence is a cis-acting regulatory sequence of a different RSV gene.

115. The recombinant RSV of claim 108, wherein a RSV promoter element is replaced by a heterologous promoter from a different RSV.

116. The recombinant RSV of claim 63, wherein the genome or antigenome incorporates a heterologous gene or genome segment from parainfluenza virus (PIV).

117. The recombinant RSV of claim 116, wherein the gene or genome segment encodes a PIV HN or F glycoprotein or immunogenic domain or epitope thereof.

118. The recombinant RSV of claim 116, wherein the genome segment encodes one or more immunogenic protein(s), protein domain(s) or epitope(s) HPIV1, HPIV2, and/or HPIV3.

119. The recombinant RSV of claim 63, wherein the genome or antigenome is further modified to encode a non-RSV molecule selected from a cytokine, a T-helper epitope, or a protein of a microbial pathogen capable of eliciting a protective immune response in a mammalian host.

120. The recombinant RSV of claim 63 which is a virus.

121. The recombinant RSV of claim 63 which is a subviral particle.

~~122. The recombinant RSV of claim 63, formulated in a dose of 103 to 106 PFU of attenuated virus.~~

~~123. A method for stimulating the immune system of an individual to induce~~ protection against respiratory syncytial virus, which comprises administering to the individual an immunologically sufficient amount of the recombinant RSV of claim 63.

124. The method of claim 123, wherein the recombinant virus is administered in a dose of 103 to 106 PFU of the attenuated RSV.

125. The method of claim 123, wherein the recombinant virus is administered to the upper respiratory tract.

126. The method of claim 125, wherein the recombinant virus is administered by spray, droplet or aerosol.

127. The method of claim 123, wherein the recombinant virus is administered to ~~an individual seronegative for antibodies to RSV or possessing transplacentally acquired maternal antibodies to RSV.~~

128. A vaccine to induce protection against RSV, which comprises an immunologically sufficient amount of the recombinant RSV of claim 63 in a physiologically acceptable carrier.

~~129. The vaccine of claim 128, formulated in a dose of 103 to 106 PFU of the attenuated RSV.~~

130. The vaccine of claim 128, formulated for administration to the upper respiratory tract by spray, droplet or aerosol.

131. The vaccine of claim 128, wherein the recombinant RSV elicits an immune response against human RSV A, human RSV B, or both.

132. An expression vector comprising an isolated polynucleotide molecule encoding a respiratory syncytial virus (RSV) genome or antigenome modified by a partial or complete gene deletion, a change in gene position, or one or more nucleotide change(s) that modulate expression of a selected gene.

133. An isolated polynucleotide molecule comprising a respiratory syncytial virus (RSV) genome or antigenome which is modified by a partial or complete gene deletion, a change in gene position, or one or more nucleotide change(s) that modulate expression of a selected gene.

134. The isolated polynucleotide molecule of claim 133, wherein a RSV gene is deleted in whole or in part.

135. The isolated polynucleotide molecule of claim 134, wherein a SH, NS1, NS2, or G gene is deleted in whole or in part.

136. The isolated polynucleotide molecule of claim 135, wherein the SH gene is deleted.

137. The isolated polynucleotide molecule of claim 135, wherein the NS1 gene is deleted.

138. The isolated polynucleotide molecule of claim 135, wherein the NS2 gene is deleted.

139. The isolated polynucleotide molecule of claim 133, wherein expression of a selected RSV gene is reduced or ablated by introduction of one or more translation termination codons.

140. The isolated polynucleotide molecule of claim 133, wherein expression of a selected RSV gene is reduced or ablated by introduction of a frame shift mutation in the gene.

141. The isolated polynucleotide molecule of claim 133, wherein expression of a selected RSV gene is modulated by introduction, modification or ablation of a translational start site within the gene.

142. The isolated polynucleotide molecule of claim 141, wherein a translational start site of the selected gene is modified or ablated to prevent efficient translation initiation at said start site.

143. The isolated polynucleotide molecule of claim 141, wherein an internal translational start site of the selected gene is modified or ablated to prevent efficient translation initiation at said start site.

144. The isolated polynucleotide molecule of claim 143, wherein an internal translational start site of the RSV G gene is ablated to prevent efficient translation initiation at said start site specifying expression of a secreted form of the G protein.

145. The isolated polynucleotide molecule of claim 141, wherein a translational start site is introduced upstream of the selected gene or internally to enhance expression of the gene.

146. The isolated polynucleotide molecule of claim 133, wherein a position of one or more gene(s) in the genome or antigenome is altered relative to a RSV promoter.

147. The isolated polynucleotide molecule of claim 133, wherein said modification within the genome or antigenome comprising a partial or complete gene deletion, a change in gene position, or one or more nucleotide change(s) that modulate expression of a selected gene specifies a change in phenotype for the resultant recombinant virus selected from: a change in growth characteristics in culture, small plaque size, attenuation in vivo,

temperature-sensitivity, cold-adaptation, host range restriction, change in antigen expression, or a change in immunogenicity.

148. The isolated polynucleotide molecule of claim 133, wherein the genome or antigenome is further modified to incorporate one or more attenuating mutation(s) present in one or more biologically derived mutant human RSV strain(s).

149. The isolated polynucleotide molecule of claim 148, wherein the genome or antigenome is further modified to incorporate at least one and up to a full complement of attenuating mutations specifying an amino acid substitution at Val267 in the RSV N gene, Glu218 and/or Thr523 in the RSV F gene, Cys319, Phe 521, Gln831, Met1169, Tyr1321 and/or His 1690 in the RSV polymerase gene L, and a nucleotide substitution in the gene-start sequence of gene M2.

150. The isolated polynucleotide molecule of claim 148, wherein the genome or antigenome incorporates at least two attenuating mutations.

151. The isolated polynucleotide molecule of claim 133, wherein the genome or antigenome comprises a partial or complete human RSV genome or antigenome of one RSV subgroup or strain combined with a heterologous gene or gene segment from a different, human or non-human RSV subgroup or strain to form a chimeric genome or antigenome.

152. The isolated polynucleotide molecule of claim 151, wherein the heterologous gene or gene segment is from a human RSV subgroup A, human RSV subgroup B, bovine RSV, or murine RSV.

153. The isolated polynucleotide molecule of claim 152, wherein the chimeric genome or antigenome comprises a partial or complete human RSV A subgroup genome or antigenome combined with a heterologous gene or gene segment from a human RSV B subgroup virus.

154. The isolated polynucleotide molecule of claim 63, wherein the chimeric genome or antigenome comprises a partial or complete RSV background genome or

antigenome of a human or bovine RSV combined with a heterologous gene or genome segment of a different RSV to form a human-bovine chimeric RSV genome or antigenome.

155. The isolated polynucleotide molecule of claim 154, wherein the chimeric genome or antigenome comprises a partial or complete human RSV background genome or antigenome combined with a heterologous gene or genome segment from a bovine RSV.

156. The isolated polynucleotide molecule of claim 133, wherein the genome or antigenome is further modified to incorporate a nucleotide deletion, insertion, substitution, rearrangement, or modification of a cis-acting regulatory sequence within the recombinant RSV genome or antigenome.

157. The isolated polynucleotide molecule of claim 156, wherein the cis-acting regulatory sequence is a gene-start (GS) signal, a gene-end (GE) signal, or a RSV promoter element.

158. The isolated polynucleotide molecule of claim 157, wherein the cis-acting regulatory sequence is a gene-start (GS) or gene-end (GE) signal which is modified, deleted, inserted or is replaced by a heterologous GS or GE signal in the genome or antigenome.

159. The isolated polynucleotide molecule of claim 158, wherein a GE signal of the RSV NS1 or NS2 gene is replaced by a corresponding GE signal of the RSV N gene.

160. The isolated polynucleotide molecule of claim 133, wherein the genome or antigenome incorporates a heterologous gene or genome segment from parainfluenza virus (PIV).

161. The isolated polynucleotide molecule of claim 133, wherein the genome or antigenome is further modified to encode a non-RSV molecule selected from a cytokine, a T-helper epitope, or a protein of a microbial pathogen capable of eliciting a protective immune response in a mammalian host.